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U.S. PATENT APPLICATION

FOR

NOVEL NIFEDIPINE COMPOSITIONS

BY

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NOVEL NIFEDIPINE COMPOSITIONS

PRIORITY

[0001] This application is a continuation-in-part of U.S. Application No. 10/276,400, filed on January 15, 2003, which is a national stage application of PCT/US01/15983, filed on May 18, 2001, which claims priority of U.S. Application No. 09/572,961, filed on May 18, 2000, now U.S. Patent No. 6,316,029. This application is also a continuation-in-part of U.S. Application No. 09/337,675, filed on June 22, 1999 (pending). Finally, this application is a continuation-in-part of U.S. Application No. 10/345,312, filed on January 16, 2003 (pending), which is a continuation of U.S. Application No. 09/715,117, filed on November 20, 2000 (now abandoned), and a continuation-in-part of 10/075,443, filed on February 15, 2002, now U.S. Patent No. 6,592,903, which is a continuation of U.S. Application No. 09/666,539, filed on September 21, 2000, now U.S. Patent No. 6,375,986. The prior disclosures are specifically incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to a novel composition of nifedipine, comprising nifedipine particles having an effective average particle size of less than about 2000 nm and at least one surface stabilizer that is preferably adsorbed to or associated with the surface of the nifedipine particles.

BACKGROUND OF THE INVENTION

I. Background Regarding Nanoparticulate Active Agent Compositions

[0003] Nanoparticulate active agent compositions, first described in U.S. Patent No. 5,145,684 ("the '684 patent"), are particles consisting of a poorly soluble therapeutic or diagnostic agent having associated with the surface thereof a non-crosslinked surface stabilizer. The '684 patent does not describe nanoparticulate compositions nifedipine.

[0004] Methods of making nanoparticulate active agent compositions are described, for example, in U.S. Patent Nos. 5,518,187 and 5,862,999, both for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,718,388, for "Continuous

Method of Grinding Pharmaceutical Substances;" and U.S. Patent No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles." These patents do not describe methods of making nanoparticulate nifedipine.

[0005] Nanoparticulate active agent compositions are also described, for example, in U.S. Patent Nos. 5,298,262 for "Use of Ionic Cloud Point Modifiers to Prevent Particle Aggregation During Sterilization;" 5,302,401 for "Method to Reduce Particle Size Growth During Lyophilization;" 5,318,767 for "X-Ray Contrast Compositions Useful in Medical Imaging;" 5,326,552 for "Novel Formulation For Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" 5,328,404 for "Method of X-Ray Imaging Using Iodinated Aromatic Propanedioates;" 5,336,507 for "Use of Charged Phospholipids to Reduce Nanoparticle Aggregation;" 5,340,564 for "Formulations Comprising Olin 10-G to Prevent Particle Aggregation and Increase Stability;" 5,346,702 for "Use of Non-Ionic Cloud Point Modifiers to Minimize Nanoparticulate Aggregation During Sterilization;" 5,349,957 for "Preparation and Magnetic Properties of Very Small Magnetic-Dextran Particles;" 5,352,459 for "Use of Purified Surface Modifiers to Prevent Particle Aggregation During Sterilization;" 5,399,363 and 5,494,683, both for "Surface Modified Anticancer Nanoparticles;" 5,401,492 for "Water Insoluble Non-Magnetic Manganese Particles as Magnetic Resonance Enhancement Agents;" 5,429,824 for "Use of Tyloxapol as a Nanoparticulate Stabilizer;" 5,447,710 for "Method for Making Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" 5,451,393 for "X-Ray Contrast Compositions Useful in Medical Imaging;" 5,466,440 for "Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents in Combination with Pharmaceutically Acceptable Clays;" 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation;" 5,472,683 for "Nanoparticulate Diagnostic Mixed Carbamic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,500,204 for "Nanoparticulate Diagnostic Dimers as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,518,738 for "Nanoparticulate NSAID Formulations;" 5,521,218 for "Nanoparticulate Iododipamide Derivatives for Use as X-Ray Contrast Agents;" 5,525,328 for

"Nanoparticulate Diagnostic Diatrizoxy Ester X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" 5,552,160 for "Surface Modified NSAID Nanoparticles;" 5,560,931 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,565,188 for "Polyalkylene Block Copolymers as Surface Modifiers for Nanoparticles;" 5,569,448 for "Sulfated Non-ionic Block Copolymer Surfactant as Stabilizer Coatings for Nanoparticle Compositions;" 5,571,536 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,573,749 for "Nanoparticulate Diagnostic Mixed Carboxylic Anydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,573,750 for "Diagnostic Imaging X-Ray Contrast Agents;" 5,573,783 for "Redispersible Nanoparticulate Film Matrices With Protective Overcoats;" 5,580,579 for "Site-specific Adhesion Within the GI Tract Using Nanoparticles Stabilized by High Molecular Weight, Linear Poly(ethylene Oxide) Polymers;" 5,585,108 for "Formulations of Oral Gastrointestinal Therapeutic Agents in Combination with Pharmaceutically Acceptable Clays;" 5,587,143 for "Butylene Oxide-Ethylene Oxide Block Copolymers Surfactants as Stabilizer Coatings for Nanoparticulate Compositions;" 5,591,456 for "Milled Naproxen with Hydroxypropyl Cellulose as Dispersion Stabilizer;" 5,593,657 for "Novel Barium Salt Formulations Stabilized by Non-ionic and Anionic Stabilizers;" 5,622,938 for "Sugar Based Surfactant for Nanocrystals;" 5,628,981 for "Improved Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents and Oral Gastrointestinal Therapeutic Agents;" 5,643,552 for "Nanoparticulate Diagnostic Mixed Carbonic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" 5,718,919 for "Nanoparticles Containing the R(-)Enantiomer of Ibuprofen;" 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions;" 5,834,025 for "Reduction of Intravenously Administered Nanoparticulate Formulation Induced Adverse Physiological Reactions;" 6,045,829 "Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,068,858 for "Methods of Making Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV)

Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,153,225 for "Injectable Formulations of Nanoparticulate Naproxen;" 6,165,506 for "New Solid Dose Form of Nanoparticulate Naproxen;" 6,221,400 for "Methods of Treating Mammals Using Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors;" 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions;" 6,267,989 for "Methods for Preventing Crystal Growth and Particle Aggregation in Nanoparticle Compositions;" 6,270,806 for "Use of PEG-Derivatized Lipids as Surface Stabilizers for Nanoparticulate Compositions;" 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate," 6,428,814 for "Bioadhesive nanoparticulate compositions having cationic surface stabilizers;" 6,431,478 for "Small Scale Mill;" 6,432,381 for "Methods for Targeting Drug Delivery to the Upper and/or Lower Gastrointestinal Tract," and 6,592,903 for "Nanoparticulate Dispersions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate," all of which are specifically incorporated by reference. In addition, U.S. Patent Application No. 20020012675 A1, published on January 31, 2002, for "Controlled Release Nanoparticulate Compositions," and WO 02/098565 for "System and Method for Milling Materials," describe nanoparticulate active agent compositions, and are specifically incorporated by reference. None of these references describe nanoparticulate compositions of nifedipine.

[0006] Amorphous small particle compositions are described, for example, in U.S. Patent Nos. 4,783,484 for "Particulate Composition and Use Thereof as Antimicrobial Agent;" 4,826,689 for "Method for Making Uniformly Sized Particles from Water-Insoluble Organic Compounds;" 4,997,454 for "Method for Making Uniformly-Sized Particles From Insoluble Compounds;" 5,741,522 for "Ultrasmall, Non-aggregated Porous Particles of Uniform Size for Entrapping Gas Bubbles Within and Methods;" and 5,776,496, for "Ultrasmall Porous Particles for Enhancing Ultrasound Back Scatter."

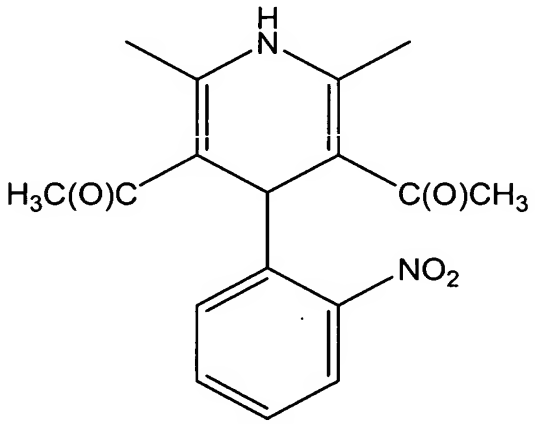
II. Background Regarding Nifedipine

[0007] Nifedipine belongs to a class of compounds known as calcium channel blockers. Nifedipine binds voltage dependent and possibly receptor operated calcium

channels in vascular smooth muscle and inhibits influx of calcium ions into vascular smooth and cardiac muscle. Nifedipine possesses outstanding vasodilating activity, especially cardiovasodilating effect, and hypotensive activity and is thus utilized widely as a vasodilating agent and a hypotensive medicament clinically for the remedy of angina pectoris and hypertension.

[0008] The mechanism by which nifedipine reduces arterial blood pressure involves peripheral arterial vasodilation and decreased peripheral vascular resistance. The mechanism by which nifedipine relieves angina has not been fully determined but is thought to include relaxation and prevention of coronary artery spasm and reduction of oxygen utilization.

[0009] Nifedipine is a yellow crystalline substance with a molecular weight of 346.3 g. The compound, which is practically insoluble in water, has the chemical name 3,5-pyridinedicarboxylic acid,1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-,dimethyl ester, $C_{17}H_{18}N_2O_6$, and the following chemical structure:



[0010] The most frequent reactions to nifedipine include hypotension, peripheral edema, enzyme level elevation, such as alkaline phosphatase, creatinine phosphokinase (CPK), lactic acid dehydrogenase (LDH), serum glutamic oxaloacetic transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT). Other adverse reactions include dizziness, flushing, headache, weakness, nausea, muscle cramps, dyspnea, nervousness, and palpitations. Nifedipine is contraindicated in individuals who have shown hypersensitivity to the drug.

[0011] Nifedipine is marketed under the trade names Procardia® (Pfizer, Inc.), Adalat® (Bayer), and others. A general dosage of nifedipine (not sustained release) for adults and children over 12 years of age is 10 mg, 3x/day. Doses above 120 mg/day are rarely needed and more than 180 mg/day is not recommended. The starting dose of nifedipine XL is 30-60 mg/day and doses above 120 mg are not recommended. *See Physicians' Desk Reference*, 57th Edition, pp. 2622-2626 (2003).

[0012] In general, nifedipine is administered to patients via an oral route. However, because nifedipine is sparingly soluble in water, conventional forms of microcrystalline nifedipine have a very poor dissolution profile.

[0013] Nifedipine is generally delivered in two patterns, *i.e.*, a quick release form and a slow release form, based upon the type of intended medical treatments. For instance, for the acute treatment of angina, it is desirable to attain relatively high nifedipine concentrations in plasma quickly and a fast release preparation of nifedipine is thus preferred. In contrast, for the treatment of hypertension, it is more desirable to maintain plasma nifedipine concentrations within a much lower concentration range and a slow release preparation of nifedipine is thus preferred.

[0014] The fast release form of nifedipine is usually a formulation consisting of an aqueous or aqueous alcoholic solution of nifedipine having a polyalkylene glycol and/or a polyoxyethylene ester component within a soft gelatin capsule. (*See e.g.*, U.S. Patent Nos. 4,978,533 and 5,200,192). The slow release form of nifedipine is prepared by dissolving microcrystalline particles of nifedipine in the presence of polyvinyl-pyrrolidone (PVP). (*See e.g.*, U.S. Patent No. 5,145,683).

[0015] U.S. Patent No. 6,106,856 for "Transdermal Delivery of Calcium Channel Blockers, Such As Nifedipine" describes methods of administering a pharmacologically-active dihydropyridine calcium channel blocker.

[0016] U.S. Patent No. 4,666,705 for "Controlled Release Formulation" describes a controlled release pharmaceutical formulation in the form of a tablet which includes an active agent and an acrylic acid polymer or copolymer. The tablet is formed via a dry granulation technique and does not require a coating.

[0017] U.S. Patent No. 4,814,175 for "Nifedipine Combination Treatment" describes a combination pharmaceutical containing nifedipine and mepindolol. The nifedipine and mepindolol are granulated separately using conventional excipients via a wet or dry granulation process. The separate granules are then placed within hard gelatin capsules for oral consumption.

[0018] To increase bioavailability of nifedipine, different techniques have been tried, namely, the transformation of nifedipine crystals into fine powder, the transformation from the crystalline to the amorphous form, the formation of clathrates or compounds of inclusion with betacyclodextrins, the formation of solid solutions with polyethylene glycols, and the formation of co-precipitates with polyvinylpyrrolidone.

[0019] For example, U.S. Patent No. 6,168,806 for "Orally Administrable Nifedipine Pellet and Process for the Preparation Thereof" describes a drug delivery system that comprises dissolving nifedipine in an organic solvent.

[0020] U.S. Patent No. 5,145,683 for "Nifedipine-Containing Pharmaceutical Compositions and Process for the Preparation Thereof" discloses nifedipine pharmaceutical compositions that have a particle size of 100 micrometers or less. Nanoparticulate nifedipine compositions according to the present invention are not taught by this patent.

[0021] Likewise, U.S. Patent No. 5,871,775 for "Controlled Release Pharmaceutical Compositions for the Oral Administration Containing Nifedipine as Active Substance" describes compositions with a granulometry lower than 100 micrometers. However, this reference does not teach nanoparticulate nifedipine compositions according to the present invention.

[0022] U.S. Patent no. 5, 543,099 for "Process to Manufacture Micronized Nifedipine Granules for Sustained Release Medicaments" describes methods for formulating sustained release tablets by micronizing an active agent to yield particles ranging in size from 0.1 micrometers to 50 micrometers. In contrast to the present invention, this reference does not teach a nifedipine composition in which at least about 50% of the particles have a size of less than about 2 microns. This is significant, as a composition having a widely variable particle size will not exhibit uniform dose response,

as the dissolution and resultant absorption of the nifedipine will correspond to the particle size of the drug (larger particles have slower dissolution and absorption and smaller particles have faster dissolution and absorption). In addition, because a majority of the particles of the prior art composition do not have a nanoparticulate particle size, the prior art composition will not exhibit the benefits described herein.

[0023] There is a need in the art for nifedipine compositions that can be readily absorbed by a human or other animal, decrease frequency of dosing, improve clinical efficacy, and potentially reduce side effects.

SUMMARY OF THE INVENTION

[0024] The present invention relates to nanoparticulate compositions comprising nifedipine. The compositions comprise nifedipine and at least one surface stabilizer preferably adsorbed on or associated with the surface of the nifedipine particles. The nanoparticulate nifedipine particles have an effective average particle size of less than about 2 microns.

[0025] Another aspect of the invention is directed to pharmaceutical compositions comprising a nanoparticulate nifedipine composition of the invention. The pharmaceutical compositions preferably comprise nifedipine, at least one surface stabilizer, and at least one pharmaceutically acceptable carrier, as well as any desired excipients. Advantages and properties of the compositions of the invention are described herein.

[0026] The invention further discloses a method of making a nanoparticulate nifedipine composition. Such a method comprises contacting nifedipine and at least one surface stabilizer for a time and under conditions sufficient to provide a nanoparticulate nifedipine composition. The one or more surface stabilizers can be contacted with nifedipine either before, preferably during, or after size reduction of the nifedipine.

[0027] The present invention is also directed to methods of treatment using the nanoparticulate nifedipine compositions of the invention for treatment of conditions typically treated with calcium channel blockers, such as angina and hypertension.

[0028] Both the foregoing general description and the following detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed. Other objects, advantages, and novel features will be readily apparent to those skilled in the art from the following detailed description of the invention.

BRIEF DESCRIPTION OF THE FIGURES

[0029] Figure 1: Shows the mean *in vivo* plasma profiles of nifedipine after single dosed, fasted, administration in humans for: (1) nanoparticulate nifedipine containing controlled release matrix tablets coated with a controlled release coating as described in Example 2; and (2) a control composition.

[0030] Figure 2: Shows the mean *in vivo* plasma profiles of nifedipine after single dosed, fasted, administration in humans for: (1) a nanoparticulate nifedipine controlled release composition manufactured as described in Example 3; and (2) a control composition.

DETAILED DESCRIPTION OF THE INVENTION

[0031] The present invention is directed to nanoparticulate compositions comprising nifedipine. The compositions comprise nifedipine and at least one surface stabilizer that is preferably adsorbed on or associated with the surface of the drug. The nanoparticulate nifedipine particles have an effective average particle size of less than about 2 microns.

[0032] As taught in the '684 patent, not every combination of surface stabilizer and active agent will result in a stable nanoparticulate active agent composition. It was surprisingly discovered that stable nanoparticulate nifedipine formulations can be made.

[0033] The current formulations of nifedipine suffer from the following problems: (1) the poor solubility of the drug results in a relatively low bioavailability; (2) dosing must be repeated several times each day; and (3) a wide variety of side effects are associated with the current dosage forms of the drug.

[0034] The present invention overcomes problems encountered with the prior art nifedipine formulations. Specifically, the nanoparticulate nifedipine formulations of the

invention may offer the following advantages as compared to conventional non-nanoparticulate nifedipine compositions: (1) faster onset of action; (2) a potential decrease in the frequency of dosing; (3) smaller doses of nifedipine required to obtain the same pharmacological effect; (4) increased bioavailability; (5) an increased rate of dissolution; (6) improved performance characteristics for oral, intravenous, subcutaneous, or intramuscular injection, such as higher dose loading and smaller tablet or liquid dose volumes; (7) improved pharmacokinetic profiles, such as improved T_{max}, C_{max}, and AUC profiles; (8) substantially similar or bioequivalent pharmacokinetic profiles of the nanoparticulate nifedipine compositions when administered in the fed versus the fasted state; (9) bioadhesive nifedipine formulations, which can coat the gut or the desired site of application and be retained for a period of time, thereby increasing the efficacy of the drug as well as eliminating or decreasing the frequency of dosing; (10) high redispersibility of the nanoparticulate nifedipine particles present in the compositions of the invention following administration; (11) low viscosity liquid nanoparticulate nifedipine dosage forms can be made; (12) for liquid nanoparticulate nifedipine compositions having a low viscosity - better subject compliance due to the perception of a lighter formulation which is easier to consume and digest; (13) for liquid nanoparticulate nifedipine compositions having a low viscosity - ease of dispensing because one can use a cup or a syringe; (14) the nanoparticulate nifedipine compositions can be used in conjunction with other active agents; (15) the nanoparticulate nifedipine compositions can be sterile filtered; (16) the nanoparticulate nifedipine compositions are suitable for parenteral administration; and (17) the nanoparticulate nifedipine compositions do not require organic solvents or pH extremes.

[0035] A preferred dosage form of the invention is a solid dosage form, although any pharmaceutically acceptable dosage form can be utilized. Exemplary solid dosage forms include, but are not limited to, tablets, capsules, sachets, lozenges, powders, pills, or granules. The solid dosage form can be, for example, a fast melt dosage form, controlled release dosage form, lyophilized dosage form, delayed release dosage form, extended release dosage form, pulsatile release dosage form, mixed immediate release and

controlled release dosage form, or a combination thereof. A solid dose tablet formulation is preferred.

[0036] The present invention is described herein using several definitions, as set forth below and throughout the application.

[0037] As used herein, "about" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term.

[0038] "Conventional" or "non-nanoparticulate active agent" shall mean an active agent which is solubilized or which has an effective average particle size of greater than about 2 microns. Nanoparticulate active agents as defined herein have an effective average particle size of less than about 2 microns.

[0039] "Pharmaceutically acceptable" as used herein refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0040] "Pharmaceutically acceptable salts" as used herein refers to derivatives wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

[0041] "Poorly water soluble drugs" as used herein means those having a solubility of less than about 30 mg/ml, preferably less than about 20 mg/ml, preferably less than about 10 mg/ml, or preferably less than about 1 mg/ml. Such drugs tend to be eliminated from the gastrointestinal tract before being absorbed into the circulation.

[0042] As used herein with reference to stable drug particles, 'stable' includes, but is not limited to, one or more of the following parameters: (1) that the nifedipine particles do not appreciably flocculate or agglomerate due to interparticle attractive forces, or otherwise significantly increase in particle size over time; (2) that the physical structure of the nifedipine particles is not altered over time, such as by conversion from an amorphous phase to crystalline phase; (3) that the nifedipine particles are chemically stable; and/or (4) where the nifedipine has not been subject to a heating step at or above the melting point of the nifedipine in the preparation of the nanoparticles of the invention.

[0043] 'Therapeutically effective amount' as used herein with respect to a drug dosage, shall mean that dosage that provides the specific pharmacological response for which the drug is administered in a significant number of subjects in need of such treatment. It is emphasized that 'therapeutically effective amount,' administered to a particular subject in a particular instance will not always be effective in treating the diseases described herein, even though such dosage is deemed a 'therapeutically effective amount' by those skilled in the art. It is to be further understood that drug dosages are, in particular instances, measured as oral dosages, or with reference to drug levels as measured in blood.

I. Preferred Characteristics of the Nanoparticulate Nifedipine Compositions of the Invention

A. Fast Onset of Activity

[0044] The use of conventional formulations of nifedipine is not ideal due to delayed onset of action. In contrast, the nanoparticulate nifedipine compositions of the invention exhibit faster therapeutic effects.

[0045] When the nanoparticulate nifedipine compositions of the invention are formulated into an oral dosage form for extended release, peak plasma concentration of

the nanoparticulate nifedipine can be obtained (T_{max}) in less than about 2.5-5 hours. In other embodiments of the invention, when the nanoparticulate nifedipine compositions of the invention are formulated into an oral dosage form for extended release, peak plasma concentration of the nanoparticulate nifedipine can be obtained in less than about 150-300 min., less than about 125-275 min., less than about 110-250 min, less than about 110 min., less than about 100 min., less than about 90 min., less than about 80 min. less than about 70 min., less than about 60 min., less than about 50 min., less than about 40 min., less than about 30 min., less than about 25 min., less than about 20 min., less than about 15 min., or less than about 10 min.

[0046] Peak blood levels after oral administration of an immediatge release nanoparticulate nifedipine composition can be obtained in less than about 30 minutes. In other embodiments of the present invention, peak plasma concentrations of nifedipine after oral administration of an immediatge release composition can be obtained in less than about 25 min., less than about 20 min., less than about 15 min., or less than about 10 min.

B. Increased Bioavailability, Frequency of Dosing, and Dosage Quantity

[0047] The nanoparticulate nifedipine compositions of the invention may preferably exhibit increased bioavailability and require smaller doses as compared to prior non-nanoparticulate nifedipine compositions, administered at the same dose.

[0048] Any drug, including nifedipine, can have adverse side effects. Thus, lower doses of nifedipine which can achieve the same or better therapeutic effects as those observed with larger doses of non-nanoparticulate nifedipine compositions, are desired. Such lower doses may be realized with the nanoparticulate nifedipine compositions of the invention because the nanoparticulate nifedipine compositions may exhibit greater bioavailability as compared to non-nanoparticulate nifedipine formulations, which means that smaller dose of nifedipine are likely required to obtain the desired therapeutic effect.

[0049] The recommended total daily dose of nifedipine (not sustained release) for adults and children over 12 years of age is 10 mg, 3x/day. Doses above 120 mg/day are rarely needed and more than 180 mg/day not recommended. The starting dose of

nifedipine XL is 30-60 mg/day and doses above 120 mg are not recommended. *See Physicians' Desk Reference*, 57th Edition, pp. 2622-2626 (2003).

[0050] In contrast, the nanoparticulate nifedipine compositions of the invention may be administered less frequently and at lower doses in dosage forms such as liquid dispersions, powders, sprays, solid re-dispersable dosage forms, ointments, creams, *etc.* Exemplary types of formulations useful in the present invention include, but are not limited to, liquid dispersions, gels, aerosols (pulmonary and nasal), ointments, creams, solid dose forms, *etc.* of nanoparticulate nifedipine. Lower dosages can be used because the small particle size of the nifedipine particles ensure greater absorption, and in the case of bioadhesive nanoparticulate nifedipine compositions, the nifedipine is retained at the desired site of application for a longer period of time as compared to conventional nifedipine dosage forms.

[0051] In one embodiment of the invention, the therapeutically effective amount of the nanoparticulate nifedipine compositions is 1/6, 1/5, ¼, 1/3rd, or ½ of the therapeutically effective amount of a non-nanoparticulate nifedipine composition.

C. Pharmacokinetic Profiles of the Nanoparticulate Nifedipine Compositions of the Invention

[0052] The invention also preferably provides nifedipine compositions having a desirable pharmacokinetic profile when administered to mammalian subjects. The desirable pharmacokinetic profile of the nifedipine compositions preferably includes, but is not limited to: (1) a T_{max} for nifedipine, when assayed in the plasma of a mammalian subject following administration, that is preferably less than the T_{max} for a non-nanoparticulate nifedipine formulation, administered at the same dosage; (2) a C_{max} for nifedipine, when assayed in the plasma of a mammalian subject following administration, that is preferably greater than the C_{max} for a non-nanoparticulate nifedipine formulation, administered at the same dosage; and/or (3) an AUC for nifedipine, when assayed in the plasma of a mammalian subject following administration, that is preferably greater than the AUC for a non-nanoparticulate nifedipine formulation, administered at the same dosage.

[0053] The desirable pharmacokinetic profile, as used herein, is the pharmacokinetic profile measured after the initial dose of nifedipine. The compositions can be formulated in any way as described below and as known to those of skill in the art.

[0054] A preferred nifedipine composition of the invention exhibits in comparative pharmacokinetic testing with a non-nanoparticulate nifedipine formulation administered at the same dosage, a T_{max} not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, not greater than about 10%, or not greater than about 5% of the T_{max} exhibited by the non-nanoparticulate nifedipine formulation.

[0055] A preferred nifedipine composition of the invention exhibits in comparative pharmacokinetic testing with a non-nanoparticulate nifedipine formulation administered at the same dosage, a C_{max} which is at least about 50%, at least about 100%, at least about 200%, at least about 300%, at least about 400%, at least about 500%, at least about 600%, at least about 700%, at least about 800%, at least about 900%, at least about 1000%, at least about 1100%, at least about 1200%, at least about 1300%, at least about 1400%, at least about 1500%, at least about 1600%, at least about 1700%, at least about 1800%, or at least about 1900% greater than the C_{max} exhibited by the non-nanoparticulate nifedipine formulation.

[0056] A preferred nifedipine composition of the invention exhibits in comparative pharmacokinetic testing with a non-nanoparticulate nifedipine formulation administered at the same dosage, an AUC which is at least about 25%, at least about 50%, at least about 75%, at least about 100%, at least about 125%, at least about 150%, at least about 175%, at least about 200%, at least about 225%, at least about 250%, at least about 275%, at least about 300%, at least about 350%, at least about 400%, at least about 450%, at least about 500%, at least about 550%, at least about 600%, at least about 750%, at least about 700%, at least about 750%, at least about 800%, at least about 850%, at least about 900%, at least about 950%, at least about 1000%, at least about 1050%, at least about 1100%, at least about 1150%, or at least about 1200% greater than the AUC exhibited by the non-nanoparticulate nifedipine formulation.

[0057] Any formulation giving the desired pharmacokinetic profile is suitable for administration according to the present methods. Exemplary types of formulations giving such profiles are liquid dispersions, gels, aerosols, ointments, creams, solid dose forms, *etc.* of nanoparticulate nifedipine.

D. The Pharmacokinetic Profiles of the Nanoparticulate Nifedipine Compositions of the Invention are Preferably not Substantially Affected by the Fed or Fasted State of the Subject Ingesting the Compositions

[0058] The invention encompasses nanoparticulate nifedipine compositions wherein preferably the pharmacokinetic profile of the nifedipine is not substantially affected by the fed or fasted state of a subject ingesting the composition. This means that there is no substantial difference in the quantity of nifedipine absorbed or the rate of nifedipine absorption when the nanoparticulate nifedipine compositions are administered in the fed versus the fasted state. Thus, the nanoparticulate nifedipine compositions of the invention can substantially eliminate the effect of food on the pharmacokinetics of nifedipine.

[0059] In another embodiment of the invention, the pharmacokinetic profile of the nifedipine compositions of the invention, when administered to a mammal in a fasted state, is bioequivalent to the pharmacokinetic profile of the same nifedipine composition administered at the same dosage, when administered to a mammal in a fed state. "Bioequivalency" is preferably established by a 90% Confidence Interval (CI) of between 0.80 and 1.25 for both C_{max} and AUC under U.S. Food and Drug Administration (USFDA) regulatory guidelines, or a 90% CI for AUC of between 0.80 to 1.25 and a 90% CI for C_{max} of between 0.70 to 1.43 under the European Medicines Evaluation Agency (EMEA) regulatory guidelines (T_{max} is not relevant for bioequivalency determinations under USFDA and EMEA regulatory guidelines).

[0060] Preferably the difference in AUC (*e.g.*, absorption) of the nanoparticulate nifedipine composition of the invention, when administered in the fed versus the fasted state, is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about

35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, or less than about 3%.

[0061] In addition, preferably the difference in C_{max} of the nanoparticulate nifedipine composition of the invention, when administered in the fed versus the fasted state, is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, or less than about 3%.

[0062] Finally, preferably the difference in the T_{max} of the nanoparticulate nifedipine compositions of the invention, when administered in the fed versus the fasted state, is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 3%, or essentially no difference.

[0063] Benefits of a dosage form which substantially eliminates the effect of food include an increase in subject convenience, thereby increasing subject compliance, as the subject does not need to ensure that they are taking a dose either with or without food.

E. Redispersibility Profiles of the Nanoparticulate Nifedipine Compositions of the Invention

[0064] An additional feature of the nanoparticulate nifedipine compositions of the invention is that the compositions redisperse such that the effective average particle size of the redispersed nifedipine particles is less than about 2 microns. This is significant, as if upon administration the nanoparticulate nifedipine particles present in the compositions of the invention did not redisperse to a substantially nanoparticulate particle size, then the dosage form may lose the benefits afforded by formulating nifedipine into a nanoparticulate particle size. In addition, drug formulations that contain a broad range of particle size affect the ability of a practitioner to adequately predict a dose-response relationship in a given subject. Thus, patient management becomes more difficult.

[0065] This is because nanoparticulate nifedipine compositions benefit from the small particle size of nifedipine; if the nanoparticulate nifedipine particles do not redisperse into the small particle sizes upon administration, then "clumps" or agglomerated nifedipine particles are formed. With the formation of such agglomerated particles, the bioavailability of the dosage form may fall.

[0066] Moreover, the nanoparticulate nifedipine compositions of the invention exhibit dramatic redispersion of the nifedipine particles upon administration to a mammal, such as a human or animal, as demonstrated by reconstitution in a biorelevant aqueous media. Such biorelevant aqueous media can be any aqueous media that exhibit the desired ionic strength and pH, which form the basis for the biorelevance of the media. The desired pH and ionic strength are those that are representative of physiological conditions found in the human body. Such biorelevant aqueous media can be, for example, aqueous electrolyte solutions or aqueous solutions of any salt, acid, or base, or a combination thereof, which exhibit the desired pH and ionic strength.

[0067] Biorelevant pH is well known in the art. For example, in the stomach, the pH ranges from slightly less than 2 (but typically greater than 1) up to 4 or 5. In the small intestine the pH can range from 4 to 6, and in the colon it can range from 6 to 8. Biorelevant ionic strength is also well known in the art. Fasted state gastric fluid has an ionic strength of about 0.1M while fasted state intestinal fluid has an ionic strength of about 0.14. *See e.g.*, Lindahl et al., "Characterization of Fluids from the Stomach and Proximal Jejunum in Men and Women," *Pharm. Res., 14* (4): 497-502 (1997).

[0068] It is believed that the pH and ionic strength of the test solution is more critical than the specific chemical content. Accordingly, appropriate pH and ionic strength values can be obtained through numerous combinations of strong acids, strong bases, salts, single or multiple conjugate acid-base pairs (*i.e.*, weak acids and corresponding salts of that acid), monoprotic and polyprotic electrolytes, *etc.*

[0069] Representative electrolyte solutions can be, but are not limited to, HCl solutions, ranging in concentration from about 0.001 to about 0.1 M, and NaCl solutions, ranging in concentration from about 0.001 to about 0.1 M, and mixtures thereof. For example, electrolyte solutions can be, but are not limited to, about 0.1 M HCl or less,

about 0.01 M HCl or less, about 0.001 M HCl or less, about 0.1 M NaCl or less, about 0.01 M NaCl or less, about 0.001 M NaCl or less, and mixtures thereof. Of these electrolyte solutions, 0.01 M HCl and/or 0.1 M NaCl, are most representative of fasted human physiological conditions, owing to the pH and ionic strength conditions of the proximal gastrointestinal tract.

[0070] Electrolyte concentrations of 0.001 M HCl, 0.01 M HCl, and 0.1 M HCl correspond to pH 3, pH 2, and pH 1, respectively. Thus, a 0.01 M HCl solution simulates typical acidic conditions found in the stomach. A solution of 0.1 M NaCl provides a reasonable approximation of the ionic strength conditions found throughout the body, including the gastrointestinal fluids, although concentrations higher than 0.1 M may be employed to simulate fed conditions within the human GI tract.

[0071] Exemplary solutions of salts, acids, bases or combinations thereof, which exhibit the desired pH and ionic strength, include but are not limited to phosphoric acid/phosphate salts + sodium, potassium and calcium salts of chloride, acetic acid/acetate salts + sodium, potassium and calcium salts of chloride, carbonic acid/bicarbonate salts + sodium, potassium and calcium salts of chloride, and citric acid/citrate salts + sodium, potassium and calcium salts of chloride.

[0072] In other embodiments of the invention, the redispersed nifedipine particles of the invention (redispersed in an aqueous, biorelevant, or any other suitable media) have an effective average particle size of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

[0073] Redispersibility can be tested using any suitable means known in the art. *See e.g.,* the example sections of U.S. Patent No. 6,375,986 for "Solid Dose

Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate."

F. Bioadhesive Nanoparticulate Nifedipine Compositions

[0074] Bioadhesive nanoparticulate nifedipine compositions of the invention comprise at least one cationic surface stabilizer, which are described in more detail below. Bioadhesive formulations of nifedipine exhibit exceptional bioadhesion to biological surfaces, such as mucous.

[0075] In the case of bioadhesive nanoparticulate nifedipine compositions, the term "bioadhesion" is used to describe the adhesion between the nanoparticulate nifedipine compositions and a biological substrate (*i.e.*, gastrointestinal mucin, lung tissue, nasal mucosa, *etc.*). *See e.g.*, U.S. Patent No. 6,428,814 for "Bioadhesive Nanoparticulate Compositions Having Cationic Surface Stabilizers," which is specifically incorporated by reference.

[0076] The bioadhesive nifedipine compositions of the invention are useful in any situation in which it is desirable to apply the compositions to a biological surface. The bioadhesive nifedipine compositions preferably coat the targeted surface in a continuous and uniform film which is invisible to the naked human eye.

[0077] A bioadhesive nanoparticulate nifedipine composition slows the transit of the composition, and some nifedipine particles would also most likely adhere to tissue other than the mucous cells and therefore give a prolonged exposure to nifedipine, thereby increasing absorption and the bioavailability of the administered dosage.

G. Low Viscosity

[0078] A liquid dosage form of a conventional microcrystalline or non-nanoparticulate nifedipine composition would be expected to be a relatively large volume, highly viscous substance which would not be well accepted by patient populations. Moreover, viscous solutions can be problematic in parenteral administration because these solutions require a slow syringe push and can stick to tubing. In addition, conventional formulations of poorly water-soluble active agents, such as nifedipine, tend

to be unsafe for intravenous administration techniques, which are used primarily in conjunction with highly water-soluble substances.

[0079] Liquid dosage forms of the nanoparticulate nifedipine compositions of the invention provide significant advantages over a liquid dosage form of a conventional microcrystalline or solubilized nifedipine composition. The low viscosity and silky texture of liquid dosage forms of the nanoparticulate nifedipine compositions of the invention result in advantages in both preparation and use. These advantages include, for example: (1) better subject compliance due to the perception of a lighter formulation which is easier to consume and digest; (2) ease of dispensing because one can use a cup or a syringe; (3) potential for formulating a higher concentration of nifedipine resulting in a smaller dosage volume and thus less volume for the subject to consume; and (4) easier overall formulation concerns.

[0080] Liquid nifedipine dosage forms which are easier to consume are especially important when considering juvenile patients, terminally ill patients, and elderly patients. Viscous or gritty formulations, and those that require a relatively large dosage volume, are not well tolerated by these patient populations. Liquid oral dosage forms can be particularly preferably for patient populations who have difficulty consuming tablets, such as infants and the elderly.

[0081] The viscosities of liquid dosage forms of nanoparticulate nifedipine according to the invention are preferably less than about 1/200, less than about 1/175, less than about 1/150, less than about 1/125, less than about 1/100, less than about 1/75, less than about 1/50, or less than about 1/25 of a liquid oral dosage form of a non-nanoparticulate nifedipine composition, at about the same concentration per ml of nifedipine.

[0082] Typically the viscosity of liquid nanoparticulate nifedipine dosage forms of the invention, at a shear rate of 0.1 (1/s), measured at 20°C, is from about 2000 mPa s to about 1 mPa s, from about 1900 mPa·s to about 1 mPa·s, from about 1800 mPa·s to about 1 mPa·s, from about 1700 mPa·s to about 1 mPa·s, from about 1600 mPa·s to about 1 mPa·s, from about 1500 mPa·s to about 1 mPa·s, from about 1400 mPa·s to about 1 mPa·s, from about 1300 mPa·s to about 1 mPa·s, from about 1200 mPa·s to about 1

mPa·s, from about 1100 mPa·s to about 1 mPa·s, from about 1000 mPa·s to about 1 mPa·s, from about 900 mPa·s to about 1 mPa·s, from about 800 mPa·s to about 1 mPa·s, from about 700 mPa·s to about 1 mPa·s, from about 600 mPa·s to about 1 mPa·s, from about 500 mPa·s to about 1 mPa·s, from about 400 mPa·s to about 1 mPa·s, from about 300 mPa·s to about 1 mPa·s, from about 200 mPa·s to about 1 mPa·s, from about 175 mPa·s to about 1 mPa·s, from about 150 mPa·s to about 1 mPa·s, from about 125 mPa·s to about 1 mPa·s, from about 100 mPa·s to about 1 mPa·s, from about 75 mPa·s to about 1 mPa·s, from about 50 mPa·s to about 1 mPa·s, from about 25 mPa·s to about 1 mPa·s, from about 15 mPa·s to about 1 mPa·s, from about 10 mPa·s to about 1 mPa·s, or from about 5 mPa·s to about 1 mPa·s. Such a viscosity is much more attractive for subject consumption and may lead to better overall subject compliance.

[0083] Viscosity is concentration and temperature dependent. Typically, a higher concentration results in a higher viscosity, while a higher temperature results in a lower viscosity. Viscosity as defined above refers to measurements taken at about 20°C. (The viscosity of water at 20°C is 1 mPa s.) The invention encompasses equivalent viscosities measured at different temperatures.

[0084] Another important aspect of the invention is that the nanoparticulate nifedipine compositions of the invention, formulated into a liquid dosage form, are not turbid. "Turbid," as used herein refers to the property of particulate matter that can be seen with the naked eye or that which can be felt as "gritty." The nanoparticulate nifedipine compositions of the invention, formulated into a liquid dosage form, can be poured out of or extracted from a container as easily as water, whereas a liquid dosage form of a non-nanoparticulate or solubilized nifedipine is expected to exhibit notably more "sluggish" characteristics.

[0085] The liquid formulations of this invention can be formulated for dosages in any volume but preferably equivalent or smaller volumes than a liquid dosage form of a non-nanoparticulate nifedipine composition.

H. Sterile Filtered Nanoparticulate Nifedipine Compositions

[0086] The nanoparticulate nifedipine compositions of the invention can be sterile filtered. This obviates the need for heat sterilization, which can harm or degrade nifedipine, as well as result in crystal growth and particle aggregation.

[0087] Sterile filtration can be difficult because of the required small particle size of the composition. Filtration is an effective method for sterilizing homogeneous solutions when the membrane filter pore size is less than or equal to about 0.2 microns (200 nm) because a 0.2 micron filter is sufficient to remove essentially all bacteria. Sterile filtration is normally not used to sterilize suspensions of micron-sized nifedipine because the nifedipine particles are too large to pass through the membrane pores.

[0088] A sterile nanoparticulate nifedipine dosage form is particularly useful in treating immunocompromised patients, infants or juvenile patients, and the elderly, as these patient groups are the most susceptible to infection caused by a non-sterile liquid dosage form.

[0089] Because the nanoparticulate nifedipine compositions of the invention, formulated into a liquid dosage form, can be sterile filtered, and because the compositions can have a very small nifedipine effective average particle size, the compositions are suitable for parenteral administration.

I. Combination Pharmacokinetic Profile Compositions

[0090] In yet another embodiment of the invention, a first nanoparticulate nifedipine composition providing a desired pharmacokinetic profile is co-administered, sequentially administered, or combined with at least one other nifedipine composition that generates a desired different pharmacokinetic profile. More than two nifedipine compositions can be co-administered, sequentially administered, or combined. While the first nifedipine composition has a nanoparticulate particle size, the additional one or more nifedipine compositions can be nanoparticulate, solubilized, or have a microparticulate particle size.

[0091] For example, a first nifedipine composition can have a nanoparticulate particle size, conferring a short T_{max} and typically a higher C_{max}. This first nifedipine

composition can be combined, co-administered, or sequentially administered with a second composition comprising: (1) nifedipine having a larger (but still nanoparticulate as defined herein) particle size, and therefore exhibiting slower absorption, a longer T_{max}, and typically a lower C_{max}; or (2) a microparticulate or solubilized nifedipine composition, exhibiting a longer T_{max}, and typically a lower C_{max}.

[0092] The second, third, fourth, *etc.*, nifedipine compositions can differ from the first, and from each other, for example: (1) in the effective average particle sizes of nifedipine; or (2) in the dosage of nifedipine. Such a combination composition can reduce the dose frequency required.

[0093] If the second nifedipine composition has a nanoparticulate particle size, then preferably the nifedipine particles of the second composition have at least one surface stabilizer associated with the surface of the drug particles. The one or more surface stabilizers can be the same as or different from the surface stabilizer(s) present in the first nifedipine composition.

[0094] Preferably where co-administration of a "fast-acting" formulation and a "longer-lasting" formulation is desired, the two formulations are combined within a single composition, for example a dual-release composition.

J. Combination Active Agent Compositions

[0095] The invention encompasses the nanoparticulate nifedipine compositions of the invention formulated or co-administered with one or more non-nifedipine active agents. Methods of using such combination compositions are also encompassed by the invention. The non-nifedipine active agents can be present in a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, or a mixture thereof.

[0096] The compound to be administered in combination with a nanoparticulate nifedipine composition of the invention can be formulated separately from the nanoparticulate nifedipine composition or co-formulated with the nanoparticulate nifedipine composition. Where a nanoparticulate nifedipine composition is co-formulated with a second active agent, the second active agent can be formulated in any suitable manner, such as immediate-release, rapid-onset, sustained-release, or dual-release form.

[0097] Such non-nifedipine active agents can be, for example, a therapeutic agent. A therapeutic agent can be a pharmaceutical agent, including a biologic. The active agent can be selected from a variety of known classes of drugs, including, for example, nutraceuticals, amino acids, proteins, peptides, nucleotides, anti-obesity drugs, central nervous system stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, such as NSAIDs and COX-2 inhibitors, anthelmintics, anti-arrhythmic agents, antibiotics (including penicillins), anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives (hypnotics and neuroleptics), astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants (expectorants and mucolytics), diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics (antiparkinsonian agents), haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones (including steroids), anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, and xanthines.

[0098] Examples of representative active agents useful in this invention include, but are not limited to, acyclovir, alprazolam, altretamine, amiloride, amiodarone, benztropine mesylate, bupropion, cabergoline, candesartan, cerivastatin, chlorpromazine, ciprofloxacin, cisapride, clarithromycin, clonidine, clopidogrel, cyclobenzaprine, cyproheptadine, delavirdine, desmopressin, diltiazem, dipyridamole, dolasetron, enalapril maleate, enalaprilat, famotidine, felodipine, furazolidone, glipizide, irbesartan, ketoconazole, lansoprazole, loratadine, loxapine, mebendazole, mercaptopurine, milrinone lactate, minocycline, mitoxantrone, nelfinavir mesylate, nimodipine, norfloxacin, olanzapine, omeprazole, penciclovir, pimozide, tacolimus, quazepam, raloxifene, rifabutin, rifampin, risperidone, rizatriptan, saquinavir, sertraline, sildenafil, acetyl-sulfisoxazole, temazepam, thiabendazole, thioguanine, trandolapril, triamterene,

trimetrexate, troglitazone, trovafloxacin, verapamil, vinblastine sulfate, mycophenolate, atovaquone, atovaquone, proguanil, ceftazidime, cefuroxime, etoposide, terbinafine, thalidomide, fluconazole, amsacrine, dacarbazine, teniposide, and acetylsalicylate.

[0099] A description of these classes of active agents and a listing of species within each class can be found in Martindale's *The Extra Pharmacopoeia,* 31st Edition (The Pharmaceutical Press, London, 1996), specifically incorporated by reference. The active agents are commercially available and/or can be prepared by techniques known in the art.

[0100] Exemplary nutraceuticals or dietary supplements include, but are not limited to, lutein, folic acid, fatty acids (*e.g.*, DHA and ARA), fruit and vegetable extracts, vitamin and mineral supplements, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids (*e.g.*, arginine, isoleucine, leucine, lysine, methionine, phenylanine, threonine, tryptophan, and valine), green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish and marine animal oils, and probiotics. Nutraceuticals and dietary supplements also include bio-engineered foods genetically engineered to have a desired property, also known as "pharmafoods."

[0101] Exemplary nutraceuticals and dietary supplements are disclosed, for example, in Roberts et al., *Nutraceuticals: The Complete Encyclopedia of Supplements, Herbs, Vitamins, and Healing Foods* (American Nutraceutical Association, 2001), which is specifically incorporated by reference. Dietary supplements and nutraceuticals are also disclosed in *Physicians' Desk Reference for Nutritional Supplements*, 1st Ed. (2001) and *The Physicians' Desk Reference for Herbal Medicines,* 1st Ed. (2001), both of which are also incorporated by reference. A nutraceutical or dietary supplement, also known as a phytochemical or functional food, is generally any one of a class of dietary supplements, vitamins, minerals, herbs, or healing foods that have medical or pharmaceutical effects on the body.

[0102] In a particularly preferred embodiment of the invention, the nanoparticulate nifedipine composition is combined with at least one other antihypertensive agent. Hypertensive agents are known in the art and are also described

in U.S. Patent No. 6,617,337, which is incorporated herein by reference in its entirety. Co-adminstration of nanoparticulate nifedipine and beta-adrenergic blocking agents are also contemplated in the present invention .

[0103] Additionally, the nanoparticulate nifedipine compositions of the present invention can be used in combination with acetylsalicylic acid (ASA) and its derivatives for the treatment of cardiovascular disorders, including angina. The nanoparticulate nifedipine compositions described herein can also be co-administered with other anti-anginal compositions such as nitrates and digitalis. ASA and derivatives thereof, nitrates and digitalis are known in the art.

[0104] The nifedipine formulations described herein can also be combined with angiotensin converting enzyme (ACE) inhibitors, such as ramipril. One of skill in the art would know which ACE inhibitors are suitable for use in the present invention.

K. Miscellaneous Benefits of the Nanoparticulate Nifedipine Compositions of the Invention

[0105] The nanoparticulate nifedipine compositions preferably exhibit an increased rate of dissolution as compared to microcrystalline or non-nanoparticulate forms of nifedipine. In addition, the nanoparticulate nifedipine compositions preferably exhibit improved performance characteristics for oral, intravenous, subcutaneous, or intramuscular injection, such as higher dose loading and smaller tablet or liquid dose volumes. Moreover, the nanoparticulate nifedipine compositions of the invention do not require organic solvents or pH extremes.

II. Nifedipine Compositions

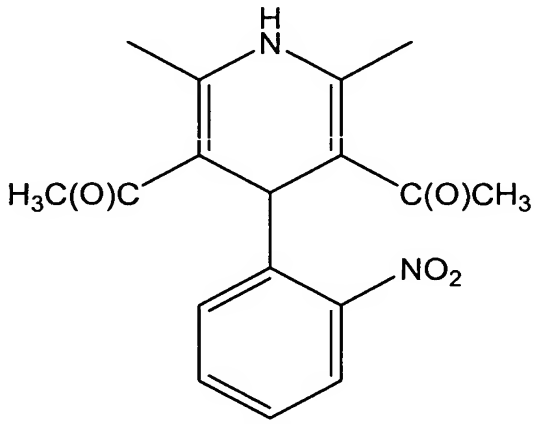
[0106] The invention provides compositions comprising nanoparticulate nifedipine particles and at least one surface stabilizer. The surface stabilizers are preferably associated with the surface of the nifedipine particles. Surface stabilizers useful herein do not chemically react with the nifedipine particles or itself. Preferably,

individual molecules of the surface stabilizer are essentially free of intermolecular cross-linkages. The compositions can comprise two or more surface stabilizers.

[0107] The present invention also includes nanoparticulate nifedipine compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers. The compositions can be formulated for parenteral injection (*e.g.*, intravenous, intramuscular, or subcutaneous), oral administration (in solid, liquid, or aerosol (*i.e.*, pulmonary) form), vaginal, nasal, rectal, ocular, local (powders, creams, ointments or drops), buccal, intracisternal, intraperitoneal, topical administration, and the like.

A. Nifedipine Particles

[0108] As used herein, "nifedipine" means 3,5-pyridinedicarboxylic acid,1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-,dimethyl ester, $C_{17}H_{18}N_2O_6$ or a salt thereof having the following chemical structure:



Derivatives of nifedipine are also encompassed by the term "nifedipine."

B. Surface Stabilizers

[0109] The choice of a surface stabilizer for nifedipine is non-trivial and required extensive experimentation to realize a desirable formulation. Accordingly, the present invention is directed to the surprising discovery that nifedipine nanoparticulate compositions can be made.

[0110] Combinations of more than one surface stabilizer can be used in the invention. Useful surface stabilizers which can be employed in the invention include, but are not limited to, known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products, and surfactants. Surface stabilizers include anionic, nonionic, cationic, zwitterionic, and ionic surfactants.

[0111] Representative examples of other useful surface stabilizers include hydroxypropyl methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, sodium lauryl sulfate, dioctylsulfosuccinate, gelatin, casein, lecithin (phosphatides), dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (*e.g.*, macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (*e.g.*, the commercially available Tweens® such as *e.g.*, Tween 20® and Tween 80® (ICI Speciality Chemicals)); polyethylene glycols (*e.g.*, Carbowaxs 3550® and 934® (Union Carbide)), polyoxyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminium silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton), poloxamers (*e.g.*, Pluronics F68® and F108®, which are block copolymers of ethylene oxide and propylene oxide); poloxamines (*e.g.*, Tetronic 908®, also known as Poloxamine 908®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.)); Tetronic 1508® (T-1508) (BASF Wyandotte Corporation), Tritons X-200®, which is an alkyl aryl polyether sulfonate (Rohm and Haas); Crodestas F-110®, which is a mixture of sucrose stearate and sucrose distearate (Croda Inc.); p-isononylphenoxypoly-(glycidol), also known as Olin-lOG® or Surfactant 10-G® (Olin Chemicals, Stamford, CT); Crodestas SL-40® (Croda, Inc.); and SA9OHCO, which is $C_{18}H_{37}CH_2(CON(CH_3)\text{-}CH_2(CHOH)_4(CH_2OH)_2$ (Eastman Kodak Co.);

decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; PEG-derivatized phospholipid, PEG- derivatized cholesterol, PEG-derivatized cholesterol derivative, PEG- derivatized vitamin A, PEG- derivatized vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, and the like.

[0112] Depending upon the desired method of administration, bioadhesive formulations of nanoparticulate nifedipine can be prepared by selecting one or more cationic surface stabilizers that impart bioadhesive properties to the resultant composition. Useful cationic surface stabilizers are described below.

[0113] Examples of useful cationic surface stabilizers include, but are not limited to, polymers, biopolymers, polysaccharides, cellulosics, alginates, phospholipids, and nonpolymeric compounds, such as zwitterionic stabilizers, poly-n-methylpyridinium, anthryul pyridinium chloride, cationic phospholipids, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide (PMMTMABr), hexyldesyltrimethylammonium bromide (HDMAB), polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, 1,2 Dipalmitoyl-sn-Glycero-3-Phosphoethanolamine-N-[Amino(Polyethylene Glycol)2000] (sodium salt) (also known as DPPE-PEG(2000)-Amine Na) (Avanti Polar Lipids, Alabaster, Al), Poly(2-methacryloxyethyl trimethylammonium bromide) (Polysciences, Inc., Warrington, PA) (also known as S1001), poloxamines such as Tetronic 908®, also known as Poloxamine 908®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.), lysozyme, long-chain polymers such as alginic acid, carrageenan (FMC Corp.), and POLYOX (Dow, Midland, MI).

[0114] Other useful cationic stabilizers include, but are not limited to, cationic lipids, sulfonium, phosphonium, and quarternary ammonium compounds, such as stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide,

coconut trimethyl ammonium chloride or bromide, coconut methyl dihydroxyethyl ammonium chloride or bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride or bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride or bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt and/or an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride and dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12}, C_{15}, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride (ALIQUAT 336™), POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters (such as choline esters of fatty acids), benzalkonium chloride, stearalkonium chloride compounds (such as stearyltrimonium chloride and Di-stearyldimonium chloride), cetyl pyridinium bromide or chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™ and ALKAQUAT™ (Alkaril Chemical Company), alkyl pyridinium salts; amines, such as alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, and vinyl pyridine, amine salts, such as lauryl amine acetate, stearyl amine acetate, alkylpyridinium

salt, and alkylimidazolium salt, and amine oxides; imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, such as poly[diallyl dimethylammonium chloride] and poly-[N-methyl vinyl pyridinium chloride]; and cationic guar.

[0115] Such exemplary cationic surface stabilizers and other useful cationic surface stabilizers are described in J. Cross and E. Singer, *Cationic Surfactants: Analytical and Biological Evaluation* (Marcel Dekker, 1994); P. and D. Rubingh (Editor), *Cationic Surfactants: Physical Chemistry* (Marcel Dekker, 1991); and J. Richmond, *Cationic Surfactants: Organic Chemistry,* (Marcel Dekker, 1990).

[0116] Nonpolymeric cationic surface stabilizers are any nonpolymeric compound, such as benzalkonium chloride, a carbonium compound, a phosphonium compound, an oxonium compound, a halonium compound, a cationic organometallic compound, a quarternary phosphorous compound, a pyridinium compound, an anilinium compound, an ammonium compound, a hydroxylammonium compound, a primary ammonium compound, a secondary ammonium compound, a tertiary ammonium compound, and quarternary ammonium compounds of the formula $NR_1R_2R_3R_4^{(+)}$. For compounds of the formula $NR_1R_2R_3R_4^{(+)}$:

(i) none of R_1-R_4 are CH_3;

(ii) one of R_1-R_4 is CH_3;

(iii) three of R_1-R_4 are CH_3;

(iv) all of R_1-R_4 are CH_3;

(v) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 is an alkyl chain of seven carbon atoms or less;

(vi) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 is an alkyl chain of nineteen carbon atoms or more;

(vii) two of R_1-R_4 are CH_3 and one of R_1-R_4 is the group $C_6H_5(CH_2)_n$, where $n>1$;

(viii) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one heteroatom;

(ix) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one halogen;

(x) two of R_1-R_4 are CH_3, one of R_1-R_4 is $C_6H_5CH_2$, and one of R_1-R_4 comprises at least one cyclic fragment;

(xi) two of R_1-R_4 are CH_3 and one of R_1-R_4 is a phenyl ring; or

(xii) two of R_1-R_4 are CH_3 and two of R_1-R_4 are purely aliphatic fragments.

[0117] Such compounds include, but are not limited to, behenalkonium chloride, benzethonium chloride, cetylpyridinium chloride, behentrimonium chloride, lauralkonium chloride, cetalkonium chloride, cetrimonium bromide, cetrimonium chloride, cethylamine hydrofluoride, chlorallylmethenamine chloride (Quaternium-15), distearyldimonium chloride (Quaternium-5), dodecyl dimethyl ethylbenzyl ammonium chloride(Quaternium-14), Quaternium-22, Quaternium-26, Quaternium-18 hectorite, dimethylaminoethylchloride hydrochloride, cysteine hydrochloride, diethanolammonium POE (10) oletyl ether phosphate, diethanolammonium POE (3)oleyl ether phosphate, tallow alkonium chloride, dimethyl dioctadecylammoniumbentonite, stearalkonium chloride, domiphen bromide, denatonium benzoate, myristalkonium chloride, laurtrimonium chloride, ethylenediamine dihydrochloride, guanidine hydrochloride, pyridoxine HCl, iofetamine hydrochloride, meglumine hydrochloride, methylbenzethonium chloride, myrtrimonium bromide, oleyltrimonium chloride, polyquaternium-1, procainehydrochloride, cocobetaine, stearalkonium bentonite, stearalkoniumhectonite, stearyl trihydroxyethyl propylenediamine dihydrofluoride, tallowtrimonium chloride, and hexadecyltrimethyl ammonium bromide.

[0118] Preferred surface stabilizers include, but are not limited to, hydroxypropylcellulose, sodium lauryl sulphate, copolymers of vinyl pyrrolidone and vinyl acetate, such as Plasdone® S630, polyvinylpyrrolidone, and mixtures thereof.

[0119] Most of these surface stabilizers are known pharmaceutical excipients and are described in detail in the *Handbook of Pharmaceutical Excipients*, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (The Pharmaceutical Press, 2000), specifically incorporated by reference. The

surface stabilizers are commercially available and/or can be prepared by techniques known in the art.

C. Pharmaceutical Excipients

[0120] Pharmaceutical compositions according to the invention may also comprise one or more binding agents, filling agents, lubricating agents, suspending agents, sweeteners, flavoring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents, and other excipients. Such excipients are known in the art.

[0121] Examples of filling agents are lactose monohydrate, lactose anhydrous, and various starches; examples of binding agents are various celluloses and cross-linked polyvinylpyrrolidone, microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102, microcrystalline cellulose, and silicified microcrystalline cellulose (ProSolv SMCC™).

[0122] Suitable lubricants, including agents that act on the flowability of the powder to be compressed, are colloidal silicon dioxide, such as Aerosil® 200, talc, stearic acid, magnesium stearate, calcium stearate, and silica gel.

[0123] Examples of sweeteners are any natural or artificial sweetener, such as sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and acsulfame. Examples of flavoring agents are Magnasweet® (trademark of MAFCO), bubble gum flavor, and fruit flavors, and the like.

[0124] Examples of preservatives are potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol, phenolic compounds such as phenol, or quarternary compounds such as benzalkonium chloride.

[0125] Suitable diluents include pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures of any of the foregoing. Examples of diluents include microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102; lactose such as lactose monohydrate, lactose anhydrous, and Pharmatose® DCL21; dibasic calcium phosphate such as Emcompress®; mannitol; starch; sorbitol; sucrose; and glucose.

[0126] Suitable disintegrants include lightly crosslinked polyvinyl pyrrolidone, corn starch, potato starch, maize starch, and modified starches, croscarmellose sodium, cross-povidone, sodium starch glycolate, and mixtures thereof.

[0127] Examples of effervescent agents are effervescent couples such as an organic acid and a carbonate or bicarbonate. Suitable organic acids include, for example, citric, tartaric, malic, fumaric, adipic, succinic, and alginic acids and anhydrides and acid salts. Suitable carbonates and bicarbonates include, for example, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, magnesium carbonate, sodium glycine carbonate, L-lysine carbonate, and arginine carbonate. Alternatively, only the sodium bicarbonate component of the effervescent couple may be present.

D. Nanoparticulate Nifedipine Particle Size

[0128] As used herein, particle size is determined on the basis of the weight average particle size as measured by conventional particle size measuring techniques well known to those skilled in the art. Such techniques include, for example, sedimentation field flow fractionation, photon correlation spectroscopy, light scattering, and disk centrifugation.

[0129] The compositions of the invention comprise nifedipine nanoparticles which have an effective average particle size of less than about 2000 nm (*i.e.*, 2 microns), less than about 1900 nm, less than less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 140 nm, less than about 130 nm, less than about 120 nm, less than about 110 nm, less than about 100 nm, less than about 90 nm, less than about 80 nm, less than about 70 nm, less than about 60 nm, or less than about 50 nm, when measured by the above-noted techniques.

[0130] By "an effective average particle size of less than about 2000 nm" it is meant that at least 50% of the nanoparticulate nifedipine particles have a weight average particle size of less than about 2000 nm, when measured by the above-noted techniques. In other embodiments of the invention, at least about 70%, at least about 90%, at least about 95%, or at least about 99% of the nanoparticulate nifedipine particles have a particle size less than the effective average, by weight, *i.e.,* less than about 2000 nm, less than about 1900 nm, less than less than about 1800 nm, less than about 1700 nm, *etc.*

[0131] If the nanoparticulate nifedipine composition is combined with a microparticulate nifedipine or non-nifedipine active agent composition, then such a composition is either solubilized or has an effective average particle size of greater than about 2 microns. By "an effective average particle size of greater than about 2 microns" it is meant that at least 50% of the microparticulate nifedipine or non-nifedipine active agent particles have a particle size greater than about 2 microns, by weight, when measured by the above-noted techniques. In other embodiments of the invention, at least about 70%, at least about 90%, at least about 95%, or at least about 99%, by weight, of the microparticulate nifedipine or non-nifedipine active agent particles have a particle size greater than about 2 microns.

[0132] In the present invention, the value for D50 of a nanoparticulate nifedipine composition is the particle size below which 50% of the nifedipine particles fall, by weight. Similarly, D90 and D99 are the particle sizes below which 90% and 99%, respectively, of the nifedipine particles fall, by weight.

E. Concentration of Nanoparticulate Nifedipine and Surface Stabilizers

[0133] The relative amounts of nifedipine and one or more surface stabilizers can vary widely. The optimal amount of the individual components can depend, for example, upon the hydrophilic lipophilic balance (HLB), melting point, and the surface tension of water solutions of the stabilizer, *etc.*

[0134] The concentration of nifedipine can vary from about 99.5% to about 0.001%, from about 95% to about 0.1%, or from about 90% to about 0.5%, by weight,

based on the total combined dry weight of the nifedipine and at least one surface stabilizer, not including other excipients.

[0135] The concentration of the at least one surface stabilizer can vary from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, or from about 10% to about 99.5%, by weight, based on the total combined dry weight of the nifedipine and at least one surface stabilizer, not including other excipients.

III. Methods of Making Nanoparticulate Nifedipine Formulations

[0136] The nanoparticulate nifedipine compositions can be made using, for example, milling, homogenization, or precipitation techniques. Exemplary methods of making nanoparticulate compositions are described in the '684 patent. Methods of making nanoparticulate compositions are also described in U.S. Patent No. 5,518,187 for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,862,999 for "Method of Grinding Pharmaceutical Substances;" U.S. Patent No. 5,665,331 for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Patent No. 5,662,883 for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Patent No. 5,560,932 for "Microprecipitation of Nanoparticulate Pharmaceutical Agents;" U.S. Patent No. 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Patent No. 5,534,270 for "Method of Preparing Stable Drug Nanoparticles;" U.S. Patent No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles;" and U.S. Patent No. 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation," all of which are specifically incorporated by reference.

[0137] Following milling, homogenization, precipitation, *etc.*, the resultant nanoparticulate nifedipine composition can be utilized in solid or liquid dosage formulations, such as controlled release formulations, solid dose fast melt formulations, aerosol formulations, nasal formulations, lyophilized formulations, tablets, capsules, solid lozenge, powders, creams, ointments, *etc.*

A. Milling to Obtain Nanoparticulate Nifedipine Dispersions

[0138] Milling nifedipine to obtain a nanoparticulate dispersion comprises dispersing nifedipine particles in a liquid dispersion media in which nifedipine is poorly soluble, followed by applying mechanical means in the presence of grinding media to reduce the particle size of nifedipine to the desired effective average particle size. The dispersion media can be, for example, water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, or glycol.

[0139] The nifedipine particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, the nifedipine particles can be contacted with one or more surface stabilizers after attrition. Other compounds, such as a diluent, can be added to the nifedipine/surface stabilizer composition during the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

B. Precipitation to Obtain Nanoparticulate Nifedipine Compositions

[0140] Another method of forming the desired nanoparticulate nifedipine composition is by microprecipitation. This is a method of preparing stable dispersions of poorly soluble active agents in the presence of one or more surface stabilizers and one or more colloid stability enhancing surface active agents free of any trace toxic solvents or solubilized heavy metal impurities. Such a method comprises, for example: (1) dissolving nifedipine in a suitable solvent; (2) adding the formulation from step (1) to a solution comprising at least one surface stabilizer; and (3) precipitating the formulation from step (2) using an appropriate non-solvent. However, in some circumstances, it may be less desireable to produce nanoparticulate nifedipine in this way since it may be expensive to remove the solvent from the nanoparticulate composition and the solvent may have some toxic effects if not all solvent is removed. The method can be followed by removal of any formed salt, if present, by dialysis or diafiltration and concentration of the dispersion by conventional means.

C. Homogenization to Obtain Nifedipine Nanoparticulate Composition

[0141] Exemplary homogenization methods of preparing active agent nanoparticulate compositions are described in U.S. Patent No. 5,510,118, for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

[0142] Such a method comprises dispersing nifedipine particles in a liquid dispersion media in which nifedipine is poorly soluble, followed by subjecting the dispersion to homogenization to reduce the particle size of the nifedipine to the desired effective average particle size. The dispersion media can be, for example, water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, or glycol.

[0143] The nifedipine particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, the nifedipine particles can be contacted with one or more surface stabilizers either before or after attrition. Other compounds, such as a diluent, can be added to the nifedipine/surface stabilizer composition either before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

IV. Methods of Using Nanoparticulate Nifedipine Formulations

[0144] The method of the invention comprises administering to a subject an effective amount of a composition comprising nanoparticulate nifedipine. The nifedipine compositions of the present invention can be administered to a subject via any conventional means including, but not limited to, orally, rectally, ocularly, parenterally (*e.g.*, intravenous, intramuscular, or subcutaneous), intracisternally, pulmonary, intravaginally, intraperitoneally, locally (*e.g.*, powders, ointments or drops), or as a buccal or nasal spray. As used herein, the term "subject" is used to mean an animal, preferably a mammal, including a human or non-human. The terms patient and subject may be used interchangeably.

[0145] Nifedipine affects the movement of calcium into heart and blood vessel cells, and causes a relaxing effect of the muscles to allow an increased amount of blood flow into the heart. The nanoparticulate nifedipine compositions of the invention are useful, for example, in treating angina pectoris (chest pain), and to help reduce blood

pressure (antihypertensive). In addition, the compositions of the invention can be used in treating any condition for which calcium channel blockers are typically utilized.

[0146] Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles including water, ethanol, polyols (propyleneglycol, polyethylene-glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0147] The nanoparticulate compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the growth of microorganisms can be ensured by various antibacterial and antifungal agents, such as parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin.

[0148] Solid dosage forms for oral administration include, but are not limited to, powder aerosols, capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active agent is admixed with at least one of the following: (a) one or more inert excipients (or carriers), such as sodium citrate or dicalcium phosphate; (b) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; (c) binders, such as carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (d) humectants, such as glycerol; (e) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (f) solution retarders, such as paraffin; (g) absorption accelerators, such as quaternary ammonium compounds; (h) wetting agents, such as cetyl alcohol and glycerol monostearate; (i) adsorbents, such as kaolin and bentonite; and (j) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium

lauryl sulfate, or mixtures thereof. For capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

[0149] Liquid dosage forms for oral administration include pharmaceutically acceptable aerosols, emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active agent, the liquid dosage forms may comprise inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers. Exemplary emulsifiers are ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, such as cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, fatty acid esters of sorbitan, or mixtures of these substances, and the like.

[0150] Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0151] One of ordinary skill will appreciate that effective amounts of nifedipine can be determined empirically and can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester, or prodrug form. Actual dosage levels of nifedipine in the nanoparticulate compositions of the invention may be varied to obtain an amount of nifedipine that is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon the desired therapeutic effect, the route of administration, the potency of the administered nifedipine, the desired duration of treatment, and other factors.

[0152] Dosage unit compositions may contain such amounts of such submultiples thereof as may be used to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors: the type and degree of the cellular or physiological response to be achieved; activity of the specific agent or composition employed; the specific agents or composition employed; the age, body weight, general health, sex, and diet of the patient; the time of administration, route of administration, and rate of excretion of the agent; the duration of the treatment;

drugs used in combination or coincidental with the specific agent; and like factors well known in the medical arts.

* * * * *

[0153] The following examples are given to illustrate the present invention. It should be understood, however, that the invention is not to be limited to the specific conditions or details described in these examples. Throughout the specification, any and all references to a publicly available document, including a U.S. patent, are specifically incorporated by reference.

Example 1

[0154] The purpose of this example was to prepare a nanoparticulate dispersion of a nifedipine composition comprising a copolymer of vinyl pyrrolidone and vinyl acetate.

An aqueous solution of 1% Plasdone® S-630 (60% vinyl pyrrolidone and 40% vinyl acetate) (ISP Technologies, Inc.) and 0.05% sodium lauryl sulfate (SLS) (Spectrum) was prepared by dissolving 0.85 g of polymer and 4.59 g of a 1% SLS solution in 75.66 g of deionized water.

[0155] The stabilizer solution was then mixed with 4.25 g of nifedipine (5% w/w) and charged into the chamber of a DYNO®-Mill Type KDL media mill (Willy Bachofen AG, Basel, Switzerland) along with 500 micron polymeric media (PolyMill® 500; Dow Chemical). The mill was operated for 2 hours.

[0156] The resultant stable nifedipine dispersion had a mean nifedipine particle size of 132 nm, with 90% of the particles having a size of less than 193 nm.

Example 2

[0157] The purpose of this example was to prepare an uncoated controlled release tablet formulation containing nanoparticulate nifedipine.

[0158] A colloidal dispersion of nifedipine in water was prepared. The dispersion contained 10 % (w/w) of nifedipine and 2 % hydroxypropyl cellulose. Particle size

analysis, performed using a Malvern Mastersizer S2.14 (Malvern Instruments Ltd., Malvern, Worcestershire, UK) recorded by a wet method using a 150 ml flow through cell, revealed the following particle size characteristics: $D_{v,90}$ 620 nm; $D_{v,50}$ 313nm; $D_{v,10}$ 170 nm, with 97.47 % of the colloidal particles being less than 1.03 μm in diameter. (Where $D_{v,90}$ 620 nm indicates that 90 % of particles had a size less than 620 nm, *etc.*).

[0159] The nifedipine dispersion was prepared for spray drying by a series of four homogenization steps. The dispersion was homogenized at medium shear for 5 min. Sodium lauryl sulphate (0.05 %) was added prior to homogenization at medium shear for a further 5 min. The dispersion was then diluted 50:50 with purified water and homogenized at medium shear for a further 10 min. Finally, mannitol (10 %) was added and the mixture was homogenized at high shear for 15 min. The final content of the mixture to be spray dried is given in Table 1.

Table 1
Composition prior to spray drying for Example 2

Ingredient	Amount (% by wt.)
Nifedipine dispersion	45.44
Purified water	45.44
Mannitol	9.09
Sodium lauryl sulphate	0.02

[0160] The mixture thus obtained was spray dried using a Büchi Mini B-191 Spray Drier system (Büchi, Switzerland). The spray drying conditions are summarized in Table 2. The spray dried nifedipine particles thus prepared were then blended. The blend formulation is given in Table 3.

Table 2
Spray drying conditions for Example 2

Parameter	Level
Inlet temperature	135 °C
Atomising pressure setting	800 l/min
Vacuum pressure	30-45 mbar
Aspirator setting	100 %
Spray rate	6 ml/min

[0161] The blend obtained after the previous step was tableted manually using a Fette E1 tablet press (Wilheim Fette GmbH, Schwarzembek, Germany) fitted with 11 mm round normal concave tooling. The tablets produced had a mean tablet hardness of 122.7 N and a mean tablet potency of 29.7 mg/ tablet. *In vitro* dissolution was carried out in phosphate - citrate buffer, pH 6.8, containing 0.5 % sodium lauryl sulphate, using USP apparatus II (100 rpm). Dissolution data is given in Table 4.

Table 3
Blend formulation for Example 2

Ingredient	Amount
Spray dried nifedipine	17.92
Avicel PH102	30.01
Pharmatose DCL	30.01
Methocel K 15M	20.00
Colloidal silicon dioxide	1.20
Magnesium stearate	0.86

Table 4
Dissolution data for uncoated nifedipine tablets prepared according to Example 2

Time (hr)	% Active Released
1.0	17.8
2.0	24.9
4.0	37.1
6.0	49.1
8.0	61.5
10.0	71.5
22.0	108.8

Example 3

[0162] The purpose of this example was to prepare a coated controlled release tablet formulation containing nanoparticulate nifedipine.

[0163] Tablets prepared according to Example 1 were coated with a Eudragit® L coating solution detailed in Table 5. Coating was performed using an Manesty

Accelacota 10" apparatus (Manesty Machine Ltd., Liverpool, UK) and a coating level of 5.5 % solids weight gain was achieved. Coating conditions are given in Table 6.

Table 5
Coating solution formulation

Ingredient	Amount (%)
Eudargit® L 12.5	49.80
Talc	2.49
Dibutyl sebecate	1.25
Isopropyl alcohol	43.46
Purified water	3.00

Table 6
Coating conditions

Parameter	Level
Inlet temperature	35 – 45 °C
Outlet temperature	32 – 36 °C
Air pressure	1.4 bar
Spray rate	27 g/min

[0164] *In vitro* dissolution was carried out according to the same methodology used in co-pending U.S. Application No. 09/337,675 for "Controlled Release of Nanoparticle Compositions," which is incorporated herein by reference in its entirety: phosphate - citrate buffer, pH 6.8, containing 0.5 % sodium lauryl sulphate, using USP apparatus II (100 rpm). Dissolution data is given in Table 7.

Table 7 Dissolution data for coated nifedipine tablets prepared according to Example 3	
Time (hr)	**% Active Released**
1.0	4.3
2.0	11.5
4.0	24.0
6.0	38.0
8.0	58.3
10.0	66.4
22.0	99.6

[0165] Figure 1 shows the mean *in vivo* plasma profiles in nine fasted human volunteers for: (1) nifedipine containing controlled release matrix tablets coated with a controlled release coating according to the present invention as described in Example 2; and (2) a control composition. The study had a fully randomized, fully crossed over, single dose administration design. From the figure it can be seen that a controlled release composition prepared according to Example 2 shows a high level of availability and shows good controlled release characteristics over a 24 hour period.

Example 4

[0166] The purpose of this example was to prepare delayed release nanoparticulate nifedipine capsules.

[0167] A colloidal dispersion of nifedipine in water was prepared. The dispersion contained 10% w/w Nifedipine, 2% hydroxypropylcellulose, and 0.1 % sodium lauryl sulphate in water. Particle size analysis, performed using a Malvern Mastersizer S2.14, recorded by a wet method using a 150 ml flow through cell, revealed the following particle size characteristics: Dv,90 = 490 nm; Dv,50 = 290 nm; Dv,10 = 170 nm.

[0168] The nifedipine dispersion was prepared for spray drying by adding Purified Water and homogenizing for 5 minutes. Mannitol was added and the resulting mixture was homogenized for 15 minutes. The final content of the mixture to be spray dried is given in Table 8.

Table 8 Composition prior to spray drying for Example 4	
Ingredient	**Amount (% by wt.)**
Nifedipine dispersion	45.45
Mannitol	9.09
Purified water	45.45

[0169] The mixture thus obtained was spray dried using a Buchi Mini B-191 Spray Drier system. The spray drying conditions are summarized in Table 9.

Table 9 Spray drying conditions for Example 4	
Parameter	**Level**
Inlet temperature	135 °C
Atomising pressure setting	800 mbar
Aspirator setting	100 %
Flow rate	6 ml/min

[0170] The spray dried nifedipine particles thus prepared were then blended. The blend formulation is given in Table 10.

Table 10 Blend formulation for Example 4	
Ingredient	**Amount (% by wt.)**
Spray dried nifedipine (Dv,90 *ca* 500 nm)	10.40
Avicel™ pH102	77.05
Explotab	10.00
Colloidal Silicon Dioxide	1.00
Magnesium stearate	1.50

[0171] The resulting blend was tableted using a Fette P2100 rotary tablet press (Wilhelm Fette GmbH, Schwarzenbek, Germany) fitted with 3.8 mm shallow concave multi-tipped tooling. The tablets had a mean set up hardness of 56 N and a mean set up weight of 34.46 mg.

[0172] The tablets thus obtained were coated in a Hi-Coater (Vector Corp., Marion, IA, USA) with the Eudragit S coating solution detailed in Table 11. A coating level of 10.03 % solids weight gain was achieved.

Table 11
Coating Solution Formulation for Example 4

Ingredient	Amount (% by wt.)
Eudragit S 12.5	50.0
Talc	2.50
Dibutyl Sebecate	1.25
Isopropyl Alcohol	43.25
Purified Water	3.00

[0173] The coated minitablets thus obtained were hand-filled into hard gelatin capsules to form Nifedipine 10 mg Capsules (9 minitablets / capsule). *In vitro* dissolution was carried out in citrate-phosphate buffer, pH 6.8, containing 0.5 % Sodium Lauryl Sulphate, using a USP apparatus II (100 rpm). The dissolution data of the resulting capsules is given in Table 12.

Table 12
Dissolution data for Nifedipine 10 mg capsules prepared according to Example 4

Time (hr)	% Active Released
0.25	3.99
0.5	4.60
0.75	21.10
1.0	93.07
1.5	100.39
2.0	100.79

Example 5

[0174] The purpose of this example was to prepare a control for delayed release nanoparticulate nifedipine capsules. The control does not contain a nanoparticulate nifedipine composition.

[0175] Nifedipine raw material (Dv, 90 = 673 μm), Explotab, and Avicel pH 102 were mixed in the Gral 25 (NV-Machines Colett SA, Wommelgam, Belgium) for 10 minutes at 1000 rpm. Purified water was gradually added with mixing until granulation was achieved. The granulate was oven dried for 18 hours at 50 °C. The dried granulate was milled through a 50 mesh screen using a Fitzmill M5A (The Fitzpatrick Co. Europe, Sint-Niklaas, Belgium). The final content of the granulate is summarized in Table 13.

Table 13
Final composition of Granulate for Example 5

Ingredient	Amount (% by wt.)
Nifedipine	7.68
Explotab	24.22
Avicel pH 102	68.10

[0176] The granulate thus obtained (Dv, 90 = 186 μm) was then blended. The blend formulation is given in Table 14.

Table 14
Blend Formulation for Example 5

Ingredient	Amount (% by wt.)
Nifedipine Granulate (Dv, 90 =186 μm)	41.28
Avicel pH102	56.22
Colloidal Silicon Dioxide	1.00
Magnesium Stearate	1.50

[0177] The particle size analysis of the starting nifedipine raw material and the milled nifedipine granulate, performed using the Malvern Mastersizer S with a 1000 mm lens (nifedipine raw material) and a 300 mm lens (milled nifedipine granulate) recorded by a dry powder method, revealed the particle size characteristics given in Table 15.

Table 15 Particle Size Analysis of Nifedipine Compositions		
Size Range	**Raw Nifedipine**	**Milled Nifedipine Granulate**
Dv, 90	673 μm	186 μm
Dv, 50	234 μm	103 μm
Dv, 10	14 μm	32 μm

[0178] The resulting blend was tableted using a Fette P2100 rotary tablet press fitted with 3.8 mm shallow concave multi-tipped tooling. The tablets had a mean set up hardness of 47 N and a mean set up weight of 35 mg. The tablets thus obtained were coated in a Hi-Coater with the Eudragit S coating solution detailed in Table 16. A coating level of 10.34 % solids weight gain was achieved.

Table 16 Coating Solution Formulation for Example 5	
Ingredient	**Amount (% by wt.)**
Eudragit S 12.5	50.0
Talc	2.50
Dibutyl Sebecate	1.25
Isopropyl Alcohol	43.25
Purified Water	3.00

[0179] The coated minitablets thus obtained were hand-filled into hard gelatin capsules to form nifedipine 10 mg capsules (9 minitablets/capsule). *In vitro* dissolution was carried out in citrate-phosphate buffer, pH 6.8, containing 0.5 % Sodium Lauryl Sulphate, using USP apparatus II (100 rpm). The dissolution data for the resulting capsules is given in Table 17.

Table 17 Dissolution data for Nifedipine 10 mg capsules prepared according to Example 5	
Time (hr)	**% Active Released**
0.25	8.83
0.5	32.50
0.75	77.88
1.0	85.26
1.5	91.30
2.0	94.46

Example 6

[0180] The purpose of this example was to compare the *in vivo* plasma profiles for a nanoparticulate nifedipine controlled release composition and a control non-nanoparticulate nifedipine controlled release composition.

[0181] Figure 2 shows the mean *in-vivo* plasma profiles of nifedipine in ten fasted human volunteers for: (1) a controlled release composition manufactured according to the present invention as described in Example 4 (nifedipine 10 mg capsules (Dv, 90 *ca* 500 nm)); and (2) a control composition manufactured as described in Example 5 (nifedipine 10 mg capsules (Dv,90 = 186 μm)). The study had a single dose, fully randomized, fully crossed over, oral administration design. From the Figure it can be seen that the controlled release composition manufactured according to the present invention shows an initial lag time followed by a rapid and high level of availability of active.

[0182] Surprisingly, the controlled release composition manufactured in accordance with the invention showed a relative bioavailability of 1.45 (*i.e.*, 45% enhanced bioavailability as compared with the control). This demonstrates the dramatic improved bioavailability of the nanoparticulate nifedipine compositions of the invention as compared to prior non-nanoparticulate nifedipine compositions.

Example 7

[0183] The purpose of this example was to prepare a fast melt formulation of nanoparticulate nifedipine.

[0184] A colloidal dispersion of nifedipine in water was prepared having 10% (w/w) nifedipine, 2% (w/w) hydroxypropyl cellulose (HPC), and 0.1 % (w/w) sodium

lauryl sulphate (SLS). Particle size analysis performed using a Malvern Mastersizer S2.14 (Malvern Instruments Ltd., Malvern, Worcestershire, UK) showed the following particle size characteristics: $D_{v,10}$ = 160 nm; $D_{v,50}$ = 290 nm; and $D_{v,90}$ = 510 nm.

[0185] The nanoparticulate nifedipine dispersion was prepared for spray drying by diluting 1:1 with purified water followed by homogenisation, and the addition of 10% (w/w) mannitol followed by homogenisation. The mixture obtained was spray-dried using a Buchi Mini B-191 spray drier system (Buchi, Switzerland).

[0186] Table 18 below shows a 10 mg nifidipine tablet formulation made by compression of the spray-dried nanoparticulate nifidipine powder.

TABLE 18
Fast Melt Nifedipine 10 mg Tablet Formulation

Material	%
Spray dried nifedipine	10.71
Mannitol	12.59
Xylitol	38.04
Citric acid	18.39
Sodium bicarbonate	18.21
Aspartame®	0.27
PEG 4000	0.89
Sodium stearyl fumerate	0.90

[0187] The fast melt 10 mg nifidipine tablet was prepared by first blending the ingredients given in the above table. The mannitol, xylitol, Aspartame®, half of the citric acid, and half of the sodium bicarbonate were mixed in a Uni-glatt (Glatt GmbH, Dresden, Germany). A 10% solution of PEG 4000 (polyethylene glycol having a molecular weight of about 4000) was used to granulate the mix at a spray rate of 10 g/min. The resultant granulate was dried for 30 minutes at about 40°C after which the remainder of the citric acid and sodium bicarbonate, the spray-dried nifedipine nanocrystals, and the sodium stearyl fumerate were added and mixed.

[0188] The resultant blend was tableted to form nifedipine 10 mg tablets using a Piccalo RTS tablet press with 10.0 mm normal concave round tooling (Piccola Industria, Argentina). The tablets produced had a mean tablet weight of 304.2 ± 3.9 mg and a mean hardness of 53.55 ± 6.85 N.

[0189] Disintegration testing was carried out on five representative tablets from each batch of tablets pressed. Disintegration testing was carried out in purified water using a VanKel disintegration apparatus (VanKel, Edison, New Jersey) at 32 oscillations per min. Results from the disintegration tests are given in Table 19 below.

TABLE 19
Disintegration Times for Fast-melt Nifedipine Tablets

Batch No.	Disintegration time (sec)				
	Tablet 1	Tablet 2	Tablet 3*	Tablet 4	Tablet 5
1	54	55	42	55	59
2	54	62	46	56	60
3	54	62	49	57	60
4	55	63	50	59	60
5	55	63	50	65	60

(*All tests were carried out at 37°C except Tablet 3 tests, which were carried out at 38°C.)

Example 8.

[0190] The purpose of this example was to prepare nanoparticulate compositions of nifedipine.

[0191] An aqueous slurry of 15% (w/w) nifedipine and 3.75% (w/w) polyvinylpyrrolidone (PVP) K29/32 was milled in a Dyno-Mill in the presence of 0.5 mm SDY-20 polystyrene media at a temperature of 10°C. Mean residence time for processing was approximately 30-45 minutes.

[0192] The resulting nifedipine particle size was measured by a Horiba LA-910 particle size analyzer (Horiba Instruments, Irvine, CA). The mean and D90 nifedipine particle sizes for batches of nifedipine milled on four different days is shown below.

Sample	Mean Nifedipine Particle Size (nm)	D90 Nifedipine Particle Size (nm)
Day 1	163	209
Day 2	206	259
Day 3	219	278
Day 4	228	287

[0193] This example demonstrates the successful preparation of stable nanoparticulate nifedipine compositions.

Example 9

[0194] The purpose of this example was to prepare nanoparticulate compositions of nifedipine.

[0195] An aqueous slurry of 20% (w/w) nifedipine and 5% (w/w) polyvinylpyrrolidone (PVP) K29/32 was milled in a Dyno-Mill in the presence of 0.5 mm SDY-20 polystyrene media at a temperature of 10°C. Mean residence time for processing was approximately 30-45 minutes.

[0196] The resulting nifedipine particle size was measured by a Horiba LA-910 particle size analyzer (Horiba Instruments, Irvine, CA). The mean nifedipine particle size was 210, with a D90 of 277.

[0197] This example demonstrates the successful preparation of stable nanoparticulate nifedipine compositions.

* * * *

[0198] It will be apparent to those skilled in the art that various modifications and variations can be made in the methods and compositions of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.